REMARKS

Applicant gratefully acknowledges the withdrawal of the restriction requirement between Groups II and III.

Claims 11-17 and 21-23 have been canceled, without prejudice, as drawn to a non-elected invention. The cancellation of these claims obviates the rejection of these claims.

Amendments to the claims are made to more clearly set forth the subject matter of the claims. The amendment to Claim 1, specifically the addition of "... is raised against ...", is made to make explicit that which is clear in the specification, namely, that the claimed antibodies are raised against one or more of the peptides selected from SEQ ID NO:1, SEQ ID NO:4 and SEQ ID NO:2 (the tetrapeptide and pentapeptides), and that it is the level of the tetrapeptide and/or pentapeptides, not that of substance P, in body fluid that inversely correlates with the magnesium binding defect. New Claims 29 and 30 read on the elected invention and have been added to further claim the invention. Support for these amendments can be found in the specification, for example, at [0027] (Claim 1) and at [0027]-[0049] (Claims 29-30). New Claim 31 requires that the claimed antibody is raised against and specifically binds one or more of the tetrapeptide and pentapeptides, but does not have significant reactivity to tachykinins of mammalian origin. Support for Claim 31 can be found in the specification, for example, it is reported that the tetrapeptide and pentapeptides are believed to be derived from degradation products of the amidated C-terminal region of tachykinins of mammalian origin, such as substance P. [0003] Further, one embodiment of the instant invention employs an antibody having affinity to the tetrapeptide and/or pentapeptide in a method to detect the amount, presence or absence of the peptide. [0026] Thus, it is implicit in this embodiment that, in order to measure the level of tetrapeptide and/or pentapeptide, the antibody not have significant reactivity to mammalian

tachykinins. Support may also be found at [0017], [0025], [0026], [0043] and [0049]. It is believed that none of these amendments constitute new matter and their entry is requested.

In the Office Action mailed October 4, 2004, the Examiner withdrew Claims 21-27 from further consideration as being drawn to a non-elected invention. However, Applicant respectfully notes that, of these claims, Claims 24-27 read on the elected invention, in as much as they depend from Claim 1 which Examiner states is under consideration in the instant application. Applicant therefore traverses the withdrawal of Claims 24-27 and requests that they be examined in the instant application along with the other claims to the elected invention.

The Office Action indicates that Claims 1-10 and 28 are drawn to an antibody that specifically binds a tachykinin peptide (page 3 of Office Action). Applicant wishes to clarify that, in fact, the present claims are limited to antibodies that are raised against and specifically bind a peptide selected from the group consisting of SEQ ID NO:1, SEQ ID NO:4, and SEQ ID NO:2. This is specifically set out in Claim 1, which is the only independent claim under consideration in the instant application.

Rejection Under 35 U.S.C. § 112

The Examiner has rejected Claims 1, 2, 7-10 and 28 under 35 U.S.C. 112, first paragraph, on the basis that the specification is not fully enabling, commensurate with the scope of the claims.

The Examiner has acknowledged that the instant specification is enabling for an antibody that specifically binds the sequence of SEQ ID NO:1 and SEQ ID NO:4. However, Examiner asserts that based on the teachings of Couraud et al., the specification is not enabling for an antibody that specifically binds SEQ ID NO:2. Applicant submits that the specification would enable one of ordinary skill in the art to practice the full breadth of the claimed invention and respectfully traverses the Examiner's rejection.

Couraud et al. describes the production and characterization of five monoclonal antibodies raised against the neuropeptide substance P. Specifically, Couraud et al. describes the generation of monoclonal antibodies by immunization with substance P conjugated to bovine serum albumin using 1,5-difluoro-2,4-dinotrobenzene (page 1709, end of first column) and the screening of hybridoma sera supernatants for anti-substance P activity utilizing immunoassays for substance P. Couraud et al. discloses use of these specific anti-substance P monoclonal antibodies as tools to study neurokinins, such as substance P, and their receptors (page 1708, second column) and, toward this objective, reports results of tests to determine which epitopes on the substance P molecule were recognized by the antibodies raised against substance P (their "fine specificities" or affinities). Couraud et al. compares the reactivity of the anti-substance P monoclonal antibodies for substance P, to their reactivity for substance P analogs, certain substance P fragments, and other tachykinins (cross-reactivities)(page 1712, bottom of right column and Table 3). From these studies, Couraud et al. reports that residues 7, 10 and 11 on the native substance P molecule were crucial for recognition by their particular anti-substance P monoclonal antibodies (pages 1709, left column, 1713, left column, and Table 3). Applicant notes that the results reported in Couraud et al. are, in part, contradicted by reports in the subsequent, commonly authored article, Dery, O. et al., Biopolymers (1996) Vol. 39, 67-74 (copy attached hereto). Specifically, Dery et al. report that the binding subsite of their anti-substance P antibodies for residues 7 and 8 on substance P are "large and deep, suitable for various side chains" (at page 74, first paragraph; see also page 72, first column)

Couraud et al. further reports that the apparent importance of the Phe^7 amino acid in native substance P molecule is consistent with the participation of that Phe^7 in an alpha helix at the core of the native molecules which provides good accessibility to the aromatic ring (page

1717, right column). Thus, Couraud et al. suggests that the antibodies that were generated to substance P recognize an epitope formed by the native substance P molecule.

As a general principal, it must be noted that the particular antibodies generated depend to a large extent on the specific immunogen and immunization procedures used. In this regard, Frickey et al. (Hybridoma, 1991, 10:6 pages 685-694, cited by the examiner in the parent case) (copy submitted herewith) is exemplary of the affect of using an alternative immunogen and immunization process on the affinities of the antibodies generated. Frickey et al. describes monoclonal antibodies raised against substance P using a different conjugate, and reports different conclusions regarding the critical epitopes for binding (page 686). Specifically, Frickey et al. states (page 692) that "a precipitous drop in potency using the 7-11 fragment of [substance P] indicated that the dipeptide, glutaminyl-glytaminyl, at the 5-6 position was an important epitope for recognition by the [anti-substance P] MAb." (Compare to Couraud et al., page 1713, column 1.)

In summary, it is urged that the failure of antibodies raised against substance P to have significant reactivity to SP 8-11, as reported in the cited reference, does not indicate a lack of enablement of an isolated antibody that is raised against and specifically binds SEQ ID NO:2. It is well known in the art that antibodies are immunoglobulins that react specifically with the antigen that stimulated their production. Thus, the fact that the Couraud et al. antibodies, raised against native substance P molecule, did not have significant reactivity for a fragment of the substance P molecule that lacks the native conformational epitope, is not surprising.

Applicant urges that only routine experimentation using art recognized methods would be required to generate the claimed antibodies. The fact that some amount of work must be performed to reach a successful end does not mean that a claimed composition is not enabled.

> "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is 'undue,' not 'experimentation.'
>
> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d 1400, 1404.

As noted in Wands, the need for routine screening is allowable and does not mean that an invention is not enabled. In the instant case, the fact that antibody positive hybridomas need to be screened for antibodies for the desired reactivity does not mean that the claimed antibodies are not enabled.

No reasons for doubting enablement for an antibody that specifically binds SEQ ID NO:2 were set forth in the Office Action other than the argument set forth in connection with Couraud et al. Examiner acknowledges that the instant specification is enabling for an antibody that specifically binds the sequence of SEQ ID NO:1 and SEQ ID NO:4. Couraud et al. describes only the particular antibodies that were raised to substance P molecule, and does not teach or suggest that additional, non-art recognized techniques would be required to generate an antibody that specifically binds a sequence corresponding to SEQ ID NO:2. Furthermore, objective enablement, not actual reduction to practice, is all that is required, as stated by the court in *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993):

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must

be relied on for enabling support. (emphasis in original) 984 F.2d at 1171-1172.

In view of the foregoing, it is urged that the instant specification enables the full breadth of the claims and requests that the rejection under 35 U.S.C. 112, first paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 101

The Examiner has rejected Claims 1-10 and 28 under 35 U.S.C. 101, second paragraph, as being directed to non-statutory subject matter.

Applicant has amended Claim 1 herein, to identify "An isolated antibody...". Claims 2-10 and 28 depend from Claim 1. Accordingly, it is believed that these claims meet the requirements of 35 U.S.C. 101, and withdrawal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102

The Examiner has rejected Claims 1-6, 9-10 and 28 under 35 U.S.C. 102 (b) as being anticipated by Couraud et al.

In response, Applicant has amended Claim 1 in order to more clearly state the subject matter of the claimed invention. Amended Claim 1 requires an isolated antibody that is raised against one or more peptide selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:4 (tetrapeptide and pentapeptides). The tetrapeptide and pentapeptides are clearly identified in the instant application as the substances of interest in normal plasma which ameliorate the magnesium binding defect in cellular membranes [0022] and [0059]. Applicant has also submitted new dependent claims to a method of producing the isolated antibody of Claim 1.

Couraud et al. discloses antibodies raised against conjugated substance P (page 1709, column 1) that are screened for anti-substance P activity (page 1710, column 1). One of the objectives stated in Couraud et al. for generating and characterizing anti-substance P antibodies

was to answer the question: What are the antigenic determinants recognized by their monoclonal antibodies on substance P? (see Page 1709, column 1)

It is well recognized in the art that antibodies react specifically with the antigen used as the immunogen. The remarkable specificity between a peptide and antibody depends on the three-dimensional structure of the peptidic backbone, the side chains, and their rotameric distributions, and the interaction of these epitopes with the hypervariable regions of the antibody. Therefore, use of the tetrapeptide and/or pentapeptide as the immunogen would be expected by one of skill in antibody art to generate antibodies having hypervariable regions distinct and apart from the antibodies described in Couraud et al.

In summary, the claims of the instant application are directed to isolated antibodies that are specific for and raised against the tetrapeptide and/or pentapeptides disclosed in the instant application. Couraud simply does not teach or suggest antibodies against these peptides. Thus, Couraud et al. does not anticipate or make obvious the claimed invention. Accordingly, withdrawal of the rejection under Section 102 (b) is respectfully requested.

In view of the foregoing amendments and remarks, it submitted that the claims remaining for active consideration in this application are free of the cited art and in condition for allowance. Accordingly, favorable action at an early date will be appreciated. If the examiner is of the view that any issue remains unresolved, it is respectfully suggested that applicants' undersigned attorney may be contacted by telephone at the number set forth below.

Respectfully submitted,

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Enclosures